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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/685,705 | 10/16/2003 | Ambati Jayakrishna | 50229-415 | 6795 |

7590 10/18/2007

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| EXAMINER | |
|---|---|
| FALK, ANNE MARIE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |
| **MAIL DATE** | **DELIVERY MODE** |
| 10/18/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| | | |
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| **Office Action Summary** | **Application No.**<br>10/685,705 | **Applicant(s)**<br>JAYAKRISHNA, AMBATI |
| | **Examiner**<br>Anne-Marie Falk, Ph.D. | **Art Unit**<br>1632 |

***-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

1)☒ Responsive to communication(s) filed on *20 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

4)☒ Claim(s) *1-28,39 and 40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

### Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 April 2007* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The amendment filed July 20, 2007 has been entered. Claims 1, 3-5, 11, 12, 14-16, 22, 23, 25, and 26 have been amended. Claims 29-38 have been canceled and Claims 39 and 40 have been newly added.

Accordingly, Claims 1-28, 39, and 40 are pending in the instant application.

The remarks filed April 12, 2007 (hereinafter referred to as "the response") are considered herein.

The elected invention is drawn to a (1) a method of screening a candidate drug in a Ccl2-deficient knockout mouse, a Ccr2-deficient knockout mouse and/or a Ccl2-deficient/Ccr2-deficient dual knockout mouse and (2) a Ccl2-deficient/Ccr2-deficient dual knockout mouse.

The rejections of Claims 3, 4, 13-15, 18-20, 23, 27, and 28 under 35 U.S.C. 112, second paragraph, for indefiniteness, are withdrawn in view of the amendments to the claims.

### *Drawings*

The drawings remain objected to because they are not of sufficient quality to permit an understanding of the invention and the results of the experiments conducted. Figures 1A, 1C, 1E, 1F, 1G, 2A-2H, 3A-3N, 4A-4F, 5A-5D, and 6E-6G, as filed on April 12, 2007, are not of sufficient quality to permit an understanding of the invention and the results of the experiments conducted. Appropriate correction is required. The color drawings have been received and are suitable for examination purposes. However, the formal black and white drawings are objected to for failure to show the relevant features described in the specification.

The drawings are objected to because of the above-noted deficiency. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to this Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

## *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

### *Enablement*

Claims 1-21 and 23-28 stand rejected and Claims 39 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a method for testing a candidate drug for treatment or prevention of age-related macular degeneration (AMD) comprising:

(i) administering the candidate drug to a Ccl2-deficient knockout mouse or a Ccr2-deficient knockout mouse, wherein said Ccl2-deficient or said Ccr2-deficient knockout mouse comprises a homozygous disruption in the endogenous Ccl2 or Ccr2 gene, respectively, such that the mouse does not express Ccl2 or Ccr2 protein, respectively, and exhibits drusen and lipofuscin deposits, retinal degeneration, and/or choroidal neovascularization in at least one eye at about nine to twenty-four months of age compared to a wild-type mouse that does not have the disrupted gene;

(ii) determining the effect of the candidate drug on drusen, lipofuscin deposition, retinal degeneration, or choroidal neovascularization in at least one eye of the mouse; and

(iii) correlating the effect of the test compound on drusen, lipofuscin deposition, retinal degeneration, or choroidal neovascularization with a potential utility to treat or prevent AMD,

does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The enablement requirement has two prongs, requiring an enabling disclosure for both how to make and how to use the claimed invention. Thus, the specification must teach how to make the claimed invention over the full scope and further must teach how to use the claimed invention over the full scope. The instant specification fails to provide an enabling disclosure teaching how to use the full scope of knockout mice as recited in the claims, for the reasons detailed herein below. The specification does not teach how to use the double knockout mouse because it does not teach the phenotype of such a mouse. Since phenotype is unpredictable for the reasons noted below, absent the teaching of a phenotype relevant to AMD, one of skill in the art would not know how to use such a mouse in the claimed screening methods. Furthermore, the specification does not teach how to use a Ccl2-deficient knockout mouse or a Ccr2-deficient knockout mouse, in the claimed methods, when the knockout mouse has a phenotype other than those noted above. The knockout mouse must exhibit a phenotypic feature of AMD to be useful in the claimed methods of screening candidate drugs for treatment of AMD.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404

(CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5) the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

**Nature of the invention and breadth of the claims.** Claim 1 is directed to a method for testing a candidate drug for treatment or prevention of age-related macular degeneration (AMD) comprising administering the candidate drug to a Ccl2-deficient knockout mouse, a Ccr2-deficient knockout mouse and/or a Ccl2-deficient/Ccr2-deficient dual knockout mouse and analyzing at least one eye for development or regression of drusen and/or lipofuscin accumulation therein, for affect of the candidate drug on Bruch's membrane, affect on retinal degeneration, in at least one eye, and/or affect on choroidal neovascularization of at least one eye. Claims 1-10, 23, and 24 do not recite any particular phenotype for the knockout mice. Thus, the claims cover the use of mice that have any phenotype at all, as well as those that have no phenotypic alteration as compared to wild-type mice. Claims 11-21 and 25-28 recite a "disrupted Ccl2 and/or CCR2 gene." The term "disrupted" covers a wide variety of different types of mutations, including any insertion, deletion, substitution, point mutation, etc. in any region of a mouse Ccl2 gene or CCR2 gene, including coding and non-coding regions. Thus, the claims cover the use of a wide variety of mutant mice. Claims 1-10, 23, and 24 recite the use of a Ccl2-deficient knockout mouse or a Ccr2-deficient knockout mouse. The claims cover the use of mice that are heterozygous for an inactivated Ccl2 or Ccr2 gene, as well as mice that are homozygous for an inactivated Ccl2 or Ccr2 gene. Given its broadest reasonable interpretation, the terms "Ccl2-deficient" and "Ccr2-deficient" cover mice that are deficient for the wild-type Ccl2 or Ccr2 protein, but does not exclude mice that express mutant forms of the Ccl2 or Ccr2 protein in place of the wild-type protein. Thus, Claims 1-10, 23, and 24, likewise cover the use of a wide variety of mutant mice, having any phenotypic alteration or no phenotypic alteration. The claims cover the use of mice that have transgene-dependent phenotypes that go beyond the dislosure, as well as mice that have no transgene-dependent phenotype at all. The claims cover the use of mice that exhibit any phenotype at all.

**Amount of direction or guidance presented and presence or absence of working examples.** The specification teaches that a homozygous gene-inactivating mutation in the mouse Ccl2 gene or Ccr2 gene coupled with the C57BL/6 genetic background produces a mouse that, as it ages, exhibits drusen and lipofuscin deposits, thickening of Bruch's membrane, retinal degeneration, and choroidal neovascularization (pages 26-32). The specification does not teach the phenotype of a mouse having the same genetic modification in the heterozygous state. Furthermore, the specification does not teach the phenotype of a mouse having both the Ccl2 and Ccr2 genes inactivated simultaneously. At page 20, the specification contemplates making a Ccl2-deficient/Ccr2-deficient double knockout mice, but the teachings of the specification are prophetic and therefore the phenotype of such a mouse is not disclosed.

Even if some interesting and useful phenotypes, not currently disclosed, are present in the Ccl2-deficient/Ccr2-deficient double knockout mouse contemplated, such phenotypes are not predictable (for the reasons discussed herein below) and the usefulness of the knockout mouse is dependent upon the mouse exhibiting a useful phenotype. The specification implies that such mice would be useful in methods for identifying candidate drugs for the treatment of AMD, but the specification does not disclose a double knockout mouse that has any of the phenotypic features of AMD.

**State of the prior art and level of predictability in the art.** The specification fails to provide an enabling disclosure for the full scope of the claimed methods, because the phenotype of a mutant mouse is unpredictable and the specification does not teach a useful phenotype for the full scope of mice covered by the claims, for the reasons discussed above. The use of a mutant mouse is dependent upon it having a **useful phenotype.** The specification does not teach how to use a mutant mouse that does not exhibit a useful knockout-dependent phenotype. For example, the specification does not teach how to use a mouse that exhibits a wild-type phenotype. Furthermore, the specification does not teach how to use a transgenic mouse of the type covered by the claims when the mouse has a phenotype that differs from the phenotype asserted or disclosed in the specification.

While gene knockout techniques are well-developed for the mouse, the phenotype of a knockout mouse is unpredictable. The claims encompass the use of mice having a wide variety of transgene-dependent phenotypes or no transgene-dependent phenotype at all. However, the skilled artisan would not know how to use such a mouse. As Doetschmann (1999) discloses "[o]ne often hears the comment that genetically engineered mice, especially knockout mice, are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype" (p. 137, column 1, paragraph 1; Laboratory Animal Science 49(2): 137-143). Minor genotypic differences can have phenotypic effects. Moens et al. (1993, Development 119: 485-499) disclose that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null. Jacks et al. (1992, Nature 359: 295-300) demonstrated an unexpected phenotype in retinoblastoma (*Rb*) gene knockout mice. Tumors were found to arise not in the retinas, as found in humans, but rather in the pituitary gland. Furthermore, only the heterozygotes are viable. Another prime example of phenotypic differences in animals having the identical gene knocked out is the HPRT gene. HPRT-deficient mice are phenotypically normal, in contrast to patients with Lesch-Nyhan syndrome, a severe neurological condition caused by HPRT deficiency in humans. The widely varying phenotypes may be the result of differences in the purine metabolism between humans and mice (see Kuehn et al., 1987, Nature 326: 295-298 and Jaenisch, 1988, Science 240: 1468-1474). Thus, the phenotype of a knockout mouse is unpredictable and phenotypic differences that vary by strain are well-documented. Even differences in the genetic background of transgenic mice can have an unpredictable effect on phenotype (Sigmund, 2000, Arterioscler. Thromb. Vasc. Biol. 20: 1425-1429). Donehower et al. (1995, Molecular Carcinogenesis 14: 16-22) have studied the effects of genetic background on tumorigenesis in p53-deficient mice. In addition to finding that genetic background alters the spectrum of tumors that develop in p53-deficient mice, the authors also demonstrated that nullizygous mice make a good lymphoma model, whereas the heterozygous mice are useful as a model of Li-Fraumeni syndrome. Oftentimes the transgenic mouse produced has no apparent transgene-dependent phenotype. See Petridou et al. (2003, Transgenic Research 12: 693-706) which discloses that their JAB transgenic mouse displayed no obvious phenotype, even at the cellular level. The combined effect of gene disruption and genetic background cannot be predicted and therefore the use of the claimed knockout mice as asserted has not been established. In the absence of specific guidance, the production of a useful transgene-dependent phenotypic alteration resulting from the disruption of a Ccl2 or Ccr2 gene (or both) as recited in the claims, is unpredictable. In the absence of specific guidance, the skilled artisan would not know how to use the claimed transgenic mice. Absent an appropriate phenotype, undue experimentation would have been required for the skilled artisan to determine how to use the double knockout mouse as claimed. Likewise, absent an appropriate phenotype, undue experimentation would have been required for the skilled artisan to determine how to use such a mouse in a method for identifying a drug useful in the treatment of AMD.

In the absence of specific guidance, one skilled in the art would not know how to use a knockout mouse that does not exhibit a specific knockout-dependent phenotype. Further, to establish a patentable utility within the context of 35 U.S.C. 101, said knockout-dependent phenotype must correlate with a specific and substantial utility. Given the state of the art, identifying a useful phenotype beyond the one already disclosed requires undue experimentation. Furthermore, one of skill in the art would not know how to use a mouse that does not exhibit one of the disclosed phenotypes, relevant to AMD, in methods for identifying a drug for the treatment of AMD.

**Relative level of skill of those in the art and quantity of experimentation necessary.** Although the level of skill in the art is high, given the high degree of unpredictability in the knockout art, the skilled artisan would be required to engage in intensive investigation, rather than routine experimentation to identify a useful phenotype in the mutant mouse and correlate it with a known disease. In view of the quantity of experimentation necessary to identify a useful phenotype beyond the one already disclosed, if any, the unpredictability of phenotypic alterations of knockout mice, and the further unpredictability of the combined effect of gene disruption and genetic background, and given the lack of applicable working examples demonstrating a useful phenotype for the full scope of mutant mice that would render the mouse a disease model, the limited guidance in the specification with regard to a relevant phenotype, the broad scope of the claims with regard to the various genotypes covered (i.e., any mutation in a Ccl2 or Ccr2 gene), and the unpredictability for using the claimed mice as set forth in the specification and claims, undue experimentation would have been required for one skilled in the art to use the full scope of mammals as claimed.

As discussed above, the disclosure provides only limited teachings with regard to a Ccl2-deficient knockout mouse and a Ccr2-deficient knockout mouse and useful phenotypes that render the mice appropriate for use in the drug screening assays. Given the broad scope of the claims and the limited guidance specific to a mouse homozygous for a gene-inactivating mutation in the Ccl2 gene or Ccr2 gene, wherein said mouse exhibits, as it ages, drusen and lipofuscin deposits, thickening of Bruch's membrane, retinal degeneration, and choroidal neovascularization, undue experimentation would have been required for one skilled in the art to prepare other mutant mice as covered by the claims and subsequently use them in the claimed methods.

At page 8 of the response, Applicants refer to the Declaration of Dr. Ambati for showing that Ccl2$^{-/-}$/Ccr2$^{-/-}$ double knockout mice were made according to the description in the specification and that the mice exhibited the expected phenotype in that they develop drusen and exhibit retinal atrophy. The Declaration of Dr. Ambati has been fully considered but is not deemed persuasive due to the poor quality of the figures accompanying the Declaration and the resulting failure to show the relevant features described in the Declaration. The Declaration refers to "yellow-white subretinal deposits" in Figure 2 (bottom of page 2 of the Declaration), but the photos provided are black and white and therefore do not show the "yellow-white subretinal deposits." Likewise, the Declaration refers to "multiple yellow-white subretinal deposits" in Figure 3 (page 3, first paragraph of Declaration), but the photos provided are black and white and therefore do not show the relevant features. Likewise, in describing Figures 5 and 6, the Declaration refers to arrowheads that point to relevant features, but no arrowheads are visible in the figures. The figures provided with the Declaration are not of sufficient quality to permit an understanding of the invention and the results of the experiments conducted. The claims have been amended to recite that the dual knockout mice exhibit lipofuscin accumulation, thickening of Bruch's membrane, and choroidal neovascularization, but there is no evidence that the dual knockout mice exhibit these phenotypes. Given that the phenotype is unpredictable, for reasons of record, the skilled artisan would have been required to engage in undue experimentation to produce mice that exhibit these phenotypes.

As a further issue, although the claims have been amended to recite a Ccl2-/- mouse, Ccr2-/- mouse, and/or a Ccl2-/-/Ccr2-/- mouse, the claims do not recite that the mouse used in the method does not express Ccl2 or Ccr2 protein.

Claim 22 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

For the reasons noted above, the phenotype of a transgenic mouse is unpredictable. The arguments noted above are incorporated herein. Although the specification contemplates making a CCL2-deficient/CCR2-deficient double knockout mouse, the specification does not disclose the phenotype of such a mouse, or if such a mouse would even be viable. While one of skill in the art could produce a double knockout mouse by cross-breeding a CCL2-deficient mouse with a CCR2-deficient mouse, absent a teaching of a useful phenotype for the double knockout mouse, the specification does not teach how to use a CCL2-deficient/CCR2-deficient double knockout mouse.

For the reasons discussed above, the Declaration does not convincingly demonstrate the phenotype of a CCL2-deficient/CCR2-deficient double knockout mouse. Since Claim 22 continues to cover Ccl2-/-/Ccr2-/- mice having any phenotype at all, including phenotypes that go beyond the disclosure as well as mice that have no transgene-dependent phenotype at all as compared to wild-type mice, the claim would remain rejected even if the deficiencies of the Declaration are corrected, because one of skill in the art would not know how to use the claimed mouse over the full scope of the claim, wherein the mouse has any phenotype at all.

### *Conclusion*

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk
**ANNE-MARIE FALK, PH.D**
**PRIMARY EXAMINER**